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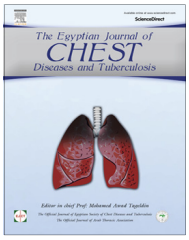

ORIGINAL ARTICLE

A study on the role of rivaroxaban in management of venous thromboembolism

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KEYWORDS

Rivaroxaban;
Anticoagulant;
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Abstract *Background:* Over 50 years the research work all over the world was concerning to find out a novel oral heparin to avoid the side effects of conventional anticoagulants as warfarin which requires changes in diet and lifestyle, regular checkup, and has a risk of severe hemorrhage. Rivaroxaban offers such advantages as oral mode of administration, more predictable anticoagulant response, greater specificity with no need for routine checkup and patient monitoring and has a uniform dose. When switching patients from warfarin to rivaroxaban, warfarin is discontinued and rivaroxaban is started as soon as INR is below 3.0 to avoid periods of inadequate anticoagulation.

Aim of the work: To study the role and suitability of oral rivaroxaban therapy in management of venous thromboembolism in Egyptian patients.

Patient and methods: This work was done over 120 mild or minor pulmonary embolism patients, divided into 2 groups, *group I* included 100 patients received oral rivaroxaban for 1 week, continued with warfarin for 6 months guided with INR measurement, *group II* included 20 patients who are financially supported and can continue with rivaroxaban for 6 months. The following was done for all patients. Clotting time (CT), D Dimer, INR, APTT, platelet count, complete liver and kidney functions, digital X ray Chest, multi-slice CT angiogram in some cases, and ECG, CK MB and troponin when needed.

Results: Our patients were divided into 2 groups, *group I* included 100 patients 54 males and 46 females with a mean age of 48.3 ± 15.43 and a mean body weight of 84.7 ± 16.4 *group II* included 20 patients 11 males and 9 females with a mean age of 45.6 ± 12.21and a mean body weight of 85.2 ± 12, the recorded side effects were minor bleeding in 11% of the cases of group I and 10% of the cases of group II, headache in 6% of the cases of group I and 5% of the cases of group II, GIT upset in 5% of the cases in both groups, dizziness in 4% of the cases of group I and 5% of the cases of group II with no statistical significant differences between the 2 arms of the study.

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Conclusion and recommendation: Rivaroxaban is a rapid onset of anticoagulant that can be given in fixed doses without routine monitoring. It can replace injectable anticoagulants as an initial treatment in management of patients with mild venous thromboembolism as it is suitable as regard the economic and the health status of the Egyptian patients.

Introduction

There is a clinical need for safe new oral anticoagulants, as the currently available anticoagulants such as vitamin K antagonists [1] and low-molecular-weight heparins (LMWHs) [2], are not targeted, which means that they inhibit more than one enzyme in the coagulation cascade. In recent years, new anticoagulants targeting single component of the coagulation cascade have been developed.

The use of warfarin reduces the rate of thromboembolic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment as its response is modified by genetic and environmental factors that can influence its absorption, pharmacokinetics, and pharmacodynamics. Rivaroxaban, is the first bioavailable orally administered direct factor Xa inhibitor, which may provide more consistent and predictable anticoagulation than warfarin [3], as it selectively and reversibly blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X plays a central role in the coagulation cascade. As factor Xa acts at the junction of the external and internal pathways of coagulation, rivaroxaban prolongs both PT and aPTT, which is dose dependent [4].

Rivaroxaban maximum plasma concentration is 30 min to 3 h, and its half-life has been reported to be 3–9 h. Rivaroxaban provides high potency and selectivity and dose-dependent inhibition of factor Xa. Two thirds of the drug is metabolized to inactive metabolites in liver, half of which is excreted by kidneys and other half is excreted via fecal route. CYP3A4, CYP345, and CYP2J2 catalyze the hepatic metabolism of rivaroxaban [5]. The other one-third is excreted unchanged by kidneys. As a significant portion of rivaroxaban is excreted via kidneys, renal impairment is expected to increase the concentration of the drug, with increasing severity of renal impairment causing more retention of the drug. Mild renal impairment (creatinine clearance 50–80 mL/min) increases the concentration (AUC) of the drug by 44%, moderate impairment (Cr CL 30–49 mL/min) by 52%, and severe impairment (Cr CL 15–29 ml/min) by 64% that is associated with more inhibition of factor Xa and more prolongation of PT. The drug is contraindicated in patients with severe renal impairment with CrCl < 15 mL/min to avoid excessive drug accumulation and bleeding [6], liver impairment (dabigatran does not undergo hepatic metabolism and may be safe in patients with hepatic disease), as well as those who are pregnant (category C drug), breastfeeding should not take rivaroxaban [7].

Aim of the work

To study the role and suitability of oral rivaroxaban therapy in management of venous thromboembolism in Egyptian patients.

Methodology

This work was done in Chest department, Tanta University, Egypt from March 2012 to December 2013 over 120 mild or minor pulmonary embolism patients divided into 2 groups, *group I* included 100 patients who received oral rivaroxaban for 7 days, in a dose 10–20 mg twice daily according to the hepatic and renal status of the patient, warfarin was added from the third day, after 1 week rivaroxaban was withdrawn, and warfarin continued for 6 months guided with INR measurement. Initial INR was done before starting warfarin, then repeated after 1 week, 2 weeks and then monthly to adjust warfarin dosage, *group II* included 20 patients who are financially supported and can continue with rivaroxaban for 6 months. The following was done for all patients: Thorough history taking, complete physical examination, clotting time (CT), D Dimer, INR, APTT, platelet count, urea and creatinine, SGPT, SGOT, direct and indirect serum bilirubin, digital X ray Chest P/A and lateral view, multi-slice CT angiogram in some cases, and ECG, CK MB and troponin when needed.*Inclusion criteria* were patients with mild or minor pulmonary embolism, haemodynamically stable, with normal O2 saturation, refusing hospitalization. *Exclusion criteria* were patients with recent or known bleeding disorders, severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months, uncontrolled hypertension, severe renal dysfunction with creatinine clearance < 30 ml/min, recent gastrointestinal bleeding due to ulceration or esophageal varices, active liver disease and pregnancy or breast-feeding.

Results

This work was done over 120 mild or minor PE patients, divided into 2 groups, *group I* included 100 patients 54 males and 46 females with a mean age of 48.3 ± 15.43 and a mean body weight of 84.7 ± 16.4 *group II* included 20 patients 11 males and 9 females with a mean age of 45.6 ± 12.21 and a mean body weight of 85.2 ± 12 .The main symptoms of our patients were dyspnea in 74.1%, chest pain in 65%, haemoptysis in 33.3%, cough in 19% and wheeze in 15%, the main risk factors for VTE were obesity in 51.6% dyslipidemia in 49.1%, smoking in 26.6%, hormonal contraceptives in 25.8% DM in 24.1%, hyper-tension in 18.3%, hypervitaminosis k in 16.6% and other cardiac disorder in 15%, the recorded side effects were minor bleeding in 11% of the cases of group I and 10% of the cases of group II, headache in 6% of the cases of group I and 5% of the cases of group II, GIT upset in 5% of the cases in both groups, dizziness in 4% of the cases of group I and 5% of the cases of group II with no statistical significant differences between the 2 arms of the study.

Table 1 Some demographic data of studied groups (Age, Sex and Body weight).

Parameters		Group I	Group II	*P*
Age		48.3 ± 15.43	45.6 ± 12.21	NS
Sex	Male	54/100 (54%)	11/20 (55%)	NS
	Female	46/100 (46%)	9/20 (45%)	NS
Body weight		84.7 ± 16.4	85.2 ± 12	NS

Table 2 Symptoms of PE in the studied patients.

+VE	No	%
Dyspnea	89	74.1
Chest pain	78	65.0
Haemoptysis	40	33.3
Cough	23	19.1
Wheeze	19	15.8

Table 3 Risk factors of pulmonary embolism of studied patients.

+VE	No	%
Obesity	62	51.6
Dyslipidemia	59	49.1
SMOKING	32	26.6
CONTRACEPTIVE	31	25.8
DM	29	24.1
HTN	22	18.3
HYPERVITAMINOSIS K	20	16.6
Other cardiac disorders	18	15

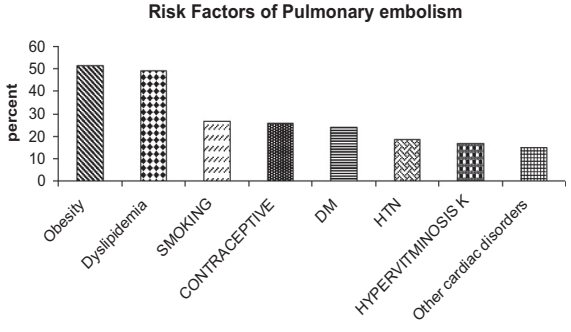

Figure 1 Risk factors of pulmonary embolism.

Table 4 Statistical comparison of the side effects of warfarin (group I) against rivaroxaban (group II).

Side effects	Group I	Group II	*P*
Minor bleeding	11/100 (11%)	2/20 (10%)	NS
Headache	6/100 (6%)	1/20 (5%)	NS
GIT upset	5/100 (5%)	1/20 (5%)	NS
Dizziness	4/100 (4%)	1/20 (5%)	NS

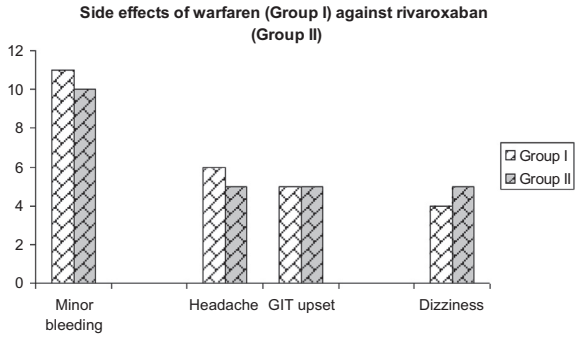

Figure 2 Side effects of warfarin (group I) against rivaroxaban (group II).

There were no significant statistical differences as regard all the side effects in both arms of the study (Tables 1–3, Fig. 1, Table 4 and Fig. 2).

Discussion

Since the 1950s, the VKA warfarin has been the gold standard in VTE treatment [8]. However, a slow onset of action, a narrow therapeutic range and variable pharmaco-kinetics (leading to unpredictable anticoagulation) make the use of warfarin challenging. Multiple food and drug interactions, dietary intake of vitamin K and genetic polymorphisms contribute to variability in the effects of warfarin. [8,9] As a result, there is a need for frequent coagulation monitoring and dose adjustment to maintain treatment within the therapeutic range [10,11]. Insufficient anticoagulation may lead to recurrent VTE, whereas excessive anticoagulation may place patients at a higher bleeding risk. [8] The onset of action of warfarin takes 36–72 h therefore, there is a need for initial bridging therapy with a fast-acting parenteral agent such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) for a minimum of 5 days [12,13] VKA therapy may begin on the first or second day of parenteral therapy and requires close INR monitoring, which should be 2.0–3.0 (target 2.5) for $\geqslant$24 h (North American guidelines) or for 2 consecutive days (European guidelines) before discontinuation of the parenteral agent [10,11]. Management of classical anticoagulants in elderly patients is challenging, due to age-related physiological changes, likelihood of co-morbidities and concomitant medications, and the increased risk of adverse events coupled with the potential difficulty for older patients to attend clinics regularly for INR monitoring, poor anticoagulation control with the classical dual-drug approach is likely [14]. Rivaroxaban is a long-awaited appealing agent because it is easy to use, does not require laboratory monitoring, and has demonstrated equivalence, or in some cases, superiority to warfarin in preventing stroke or systemic embolism in at-risk population [15].

Rivaroxaban is, at present the only one of the new oral anticoagulants that is FDA approved for the treatment of DVT and PE. It is also approved as a prophylaxis of DVT and PE after hip and knee replacement surgery, and also as a prophylaxis of stroke and other thrombo-embolic manifestations in patients with AF [16,17].

Minor side effects include headache, hypotension, dizziness, tachycardia, vomiting, edema; people who took a higher dose

were more likely to suffer from bleeding. Also patients who suddenly stop taking rivaroxaban can be at increased risk for developing thromboembolic disorders. One of the most serious side effects of rivaroxaban is bleeding and anemia, reduced platelet levels, abnormal liver function. Concomitant use of drugs affecting coagulation (eg, platelet aggregation inhibitors, other antithrombotic agents, fibrinolytic therapy) can increase the risk of bleeding [12].

Recombinant, modified factor Xa molecule is being developed as a direct reversal agent (antidote) for patients receiving a Factor Xa inhibitor who suffer a major bleeding episode or who require emergency surgery. It stops the activity of anti-Xa anticoagulant, making a patient's own factor Xa available again to participate in the coagulation process [18].

Conclusion and recommendation

Rivaroxaban has a rapid onset of anticoagulant activity, with a low potential for interactions with diet and other drugs. It can be given in fixed doses and does not require routine monitoring. It can replace injectable anticoagulants as an initial treatment in management of patients with mild venous thromboembolism as it is suitable as regard the economic and the health status for the Egyptian patients.

Conflict of interest

We have no conflict of interest to declare.

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